REMARKS

Claims 106-110, 112-118 and 120-123 are pending. Claims 101-105, 111 and 119 have been canceled without prejudice.

Claim 106 has been amended to recite that the vesicle has a size of 50 to 500 nm. Support for this amendment can be found throughout the specification and claims as originally filed. For example, at Page 10, lines 1-5. Claims 122 and 123 have been added. Support for these claims can be throughout the specification and claims as originally filed. For example, at Page 10, lines 1-5. Claim 116 has been amended to correct an inadvertent typographical error. No new matter has been added

Reconsideration and withdrawal of the rejections of this application in view of the remarks herewith, is respectfully requested, as the application is believed to be in condition for allowance.

The right to prosecute any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications is respectfully reserved.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 116-118 stand rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject mater regarded as the invention. In particular, the Office Action states that the term "further consists essentially of" is inconsistent with the language of the parent claim.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, (CCPA 1976).

It is respectfully submitted that the inclusion of one or more consistency modifiers and/or one or more antioxidants in the vesicles of claim 106 does not materially affect the basic and novel characteristics of the vesicles of the presently claimed methods. As such, the language "further consists essentially of" is not inconsistent with the language of the parent claim. Thus, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 106-110, 112-118 and 120-121 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Vyas *et al., J. Microencapsulation*, 1995, 12(2), 149-154 ("Vyas"), United States Patent No. 5,585,109 to Hayward *et al.* ("Hayward"), or United States Patent No. 4,937,254 to Sheffield *et al.* ("Sheffield") in combination with United States Patent No. 4,897,269 to Mezei ("Mezei").

As stated above, claim 106 has been amended to recite that the vesicle has a size of 50 to 500 nm. Vyas's multilamellar liposomes, on the other hand, were screened to have an average size of 1-5 μm (1000-5000 nm) and had an actual size ranging from *about 4-5 μm* (*about 4000-5000 nm*) (See, Table 1). Moreover, Vyas states "[o]n ultrasound application, drug release was increased and found to be dependent on liposomal size and percent drug entrapment" (Vyas, Page 153) and concludes that the liposomal formulation OL_3, having the largest size (5.09 ± 0.31 μm) and encapsulation, showed the most effectiveness *in vivo* (Table 4, entry 3). In stark contrast to the liposomes of Vyas, which suggests that smaller liposomes are inferior to larger ones, the vesicles of the presently claimed methods *have a size of 50-500 nm.* As such, one of ordinary skill in the art would have lacked any expectation of success in using the vesicles of the present methods which, in addition to consisting essentially of a salt of an NSAID, also have a significantly smaller size of 50 to 500 nm (0.05 to 0.5 μm).

Sheffield expressly states "the use of [multilamellar vesicles] of comparatively large size (e.g., from about 1 to about 5 microns) appears to be preferable in order to increase the dwell time of the

vesicle containing the NSAID in the peritoneal cavity (or other body cavity)" (Column 6, lines 33-37). As such, Sheffield clearly teaches away from the administration of vesicles that have a size of 50 to 500 nm (0.05 to 0.5 μm). A reference that teaches away can defeat a finding of obviousness. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-1350 (Fed. Cir. 2000). Therefore, Sheffield cannot be relied on for obviousness.

Hayward relates to "a cosmetic composition and salicylic acid delivery system [that] includes membrane lipid bylayers formed as liposomes and ***un-neutralized*** salicylic acid localized within the lipidic bylayers of the liposomes," (Abstract) (emphasis added). Hayward states "[t]he advantages of the [Hayward] invention include the fact that the cosmetic composition has the unexpected ability to sustain a neutral pH (7.0) in the external aqueous milieu, ***without neutralizing the salicylic acid to the corresponding salicylate***" (Column 4, lines 26-31) (emphasis added). Hayward further states "the present invention relates to a cosmetic dispersion that allows for the incorporation of large amounts of salicyclic acid within the hydrophobic compartment of the liposomal bilayer ***without the necessity of pre-neutralization or salt formation of the corresponding salicylate***..." (Column 1, lines 15-20) (emphasis added). Hayward also states that "[t]he formation of salts of salicylic acid, such as sodium salicylate formed by the combination of salicylic acid and sodium hydroxide, greatly improves the water solubility of the free acid, but ***substantially modifies the biological response*** to salicylic acid." (Column 1, lines 30-34) (emphasis added). As such, one of ordinary skill in the art would understand that Hayward clearly teaches away from the use of a salt of a NSAID as presently claimed.

The Office Action states that the pH of the present invention can be between 3 and 12, more particularly between 6 and 8 and thus, the pH can be less than neutral and thus the NSAIDs will be in protonated form. The Office Action therefore suggests that at any pH that is less than neutral, all of the NSAID present will be in its acid form. This is incorrect. Indeed, it is known that the pKa of most NSAIDs is between 3 and 5 (Bosek *et al, Journal Annals of Surgical Oncology*, 3(1): 62-66 (1996), see abstract attached as Exhibit A). As such, based on the Henderson-Hasselbach equation

$(pH = pKa + log_{10}[(A^-)/(HA)])$, an NSAID whose pKa = 5 will be present in at least some salt form, if not predominantly in the salt form[1], even at pH=3.

The vesicles of the presently claimed invention consist essentially of *a salt of an NSAID;* the vesicles of Hayward, on the other hand, comprise salicylic acid in *its acid form.* As such, Hayward clearly teaches away from the use of any neutralized salicylic acid (salicylate salt). As stated above, a reference that teaches away can defeat a finding of obviousness. *Winner*, 202 F.3d at 349-1350. Therefore, Hayward cannot be relied on for obviousness.

The Office Action relies on Mezei only for a suggestion, if any, of adding benzyl alcohol as a preservative or an antioxidant to a vesicular composition. The addition of benzyl alcohol does not remedy the deficiencies of Vyas, Sheffield or Hayward. Specifically, even with benzyl alcohol added, the vesicles described by Vyas or Sheffield would still be larger than the claimed vesicle size. Similarly, even with benzyl alcohol added, the vesicles described by Hayward would still teach away from the use of a salt of an NSAID. Accordingly, Vyas, Sheffield or Hayward, even in combination with Mezei, does not provide the presently claimed methods.

In view of the above, the presently claimed subject matter is not obvious over the cited references. Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103(a) of Claims 106-110, 112-118 and 120-121 is respectfully requested.

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[1] In the Henderson-Hasselbach equation, $pH - pKa = log_{10}[(A^-)/(HA)]$, wherein (A^-) is the concentration of salt present and (HA) is the concentration of free acid. Thus:

if pH = 7 and pKa = 3, then the ratio of salt to free acid will be 10000:1 ($log_{10}(10000/1) = 4$);

if pH = 3 and pKa = 3 then the ratio of salt to free acid will be 1:1 ($log_{10}(1/1) = 0$);

if pH = 3 and pKa = 4, the ratio of salt to free acid will be 1:10 ($log_{10}(1/10) = -1$); and

if pH = 3 and pKa = 5, the ratio of salt to free acid will be 1:100 ($log_{10}(1/100) = -2$).

CONCLUSION

In view of the amendments and remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 35946.701.831).

Respectfully submitted,

Dated: February 28, 2008

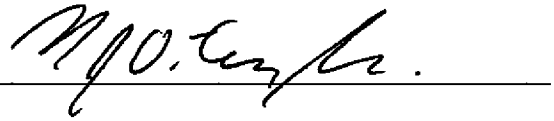
By 

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EXHIBIT A

Journal Article

Comparison of analgesic effect of locally and systemically administered ketorolac in mastectomy patients

Journal	Annals of Surgical Oncology
Publisher	Springer New York
ISSN	1068-9265 (Print) 1534-4681 (Online)
Issue	Volume 3, Number 1 / January, 1996
Category	Original Articles
DOI	10.1007/BF02409053
Pages	62-66
Subject Collection	Medicine
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Abstract **Background:** Ketorolac is a parenteral nonsteroidal antiinflammatory drug (NSAID). Two features have limited its clinical utility: tendency to elicit kidney failure and inability to produce complete analgesia. Because most NSAIDs are weak acids (pKa 3–5) and become concentrated in acidic tissues, such as injured and inflamed tissues, we hypothesized that local administration may enhance its analgesic efficacy while lowering the potential for systemic complications.

Methods: We conducted a randomized, placebo-controlled study of 60 group I–III (American Society of Anesthesiology criteria) mastectomy patients, 20 in each group. Near the end of surgery and every 6 h postoperatively, 20 ml of the study solution containing normal saline with or without 30 mg of ketorolac were administered simultaneously either via a Jackson-Pratt drain or intravenously in a double-blind fashion. The quality of pain control, the amount and character of the drain fluid, incidence of nausea and vomiting, length of stay in the postoperative care unit, and amount of morphine used for treatment of breakthrough pain were recorded.

Results: Intraoperative administration of ketorolac resulted in better quality of pain control in the immediate postoperative period regardless of route of administration. The incidence of nausea was significantly higher in the placebo group, and drain output in the ketorolac groups did not exceed the output in the placebo group.

Conclusion: Analgesic of the locally administered ketorolac is equally effective to the efficacy of ketorolac administered intravenously.

Key Words Outpatient surgery - Mastectomy - Analgesia - Ketorolac - Local effect

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